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(54) Title: CONTROLLED RELEASE POLYMERIC COMPOSITIONS OF BONE GROWTH PROMOTING COMPOUNDS

(57) Abstract: The present invention is directed to an improved system for controlled release of a bone growth promoting compound and to a flowable composition for its formation. The flowable composition is composed of a bone growth promoting compound, a thermoplastic polymer and an organic solvent. The flowable composition is capable of forming a biodegradable and/or bioerodible microporous, solid polymer matrix. The matrix is useful as an implant in patients (humans and animals) for delivery of a bone growth promoting compound to certain tissues.

CONTROLLED RELEASE POLYMERIC COMPOSITIONS OF BONE GROWTH PROMOTING COMPOUNDS

FIELD OF THE INVENTION

The invention is directed to an improved system for the controlled release of a bone growth promoting compound and to a flowable composition for its formation. The flowable composition is composed of a thermoplastic polymer, a bone growth promoting compound and an organic solvent. The flowable composition is capable of forming a biodegradable and/or bioerodible microporous, solid polymer matrix. The matrix is useful as an implant in patients (humans and animals) for delivery of a bone growth promoting compound to bone tissues.

BACKGROUND OF THE INVENTION

Biodegradable polymers are useful in many medical applications, especially drug delivery devices. Many of the biodegradable polymers used are of the thermoplastic type. Polymers made of thermoplastic resins typically liquify or soften at elevated temperatures and resolidify upon cooling. This type of polymer is generally formed into the desired structure for use as sutures, surgical clips, staples, implants and the like, prior to insertion into the body. Once inserted into the body, these polymers retain their shape.

For drug delivery devices, the drug is generally incorporated into the polymeric composition and formed into the desired shape outside the body. This solid implant is then typically inserted into the body of a human, animal, bird or the like through an incision. Alternatively, small discrete particles composed of these polymers can be injected into the body by a syringe. Preferably, however, certain of these polymers can be injected via syringe as a flowable polymeric composition.

Flowable polymeric compositions for use as biodegradable controlled release drug delivery systems are described in the patent literature, e.g., U.S. Pat. Nos. 4,938,763; 5,077,049; 5,324,519; 5,632,727; 5,599,552; 5,702,716; 5,487,897; 5,660,849; 5,278,201; 5,198,220; 5,447,725; 5,242,910; 5,733,950; 5,739,176; 5,945,115; 5,744,153; 5,759,563; 5,660,849; and 6,143,314.

These compositions are administered to the body in a flowable physical state, typically via syringe. Once in the body the composition transforms into a solid. One type of polymeric composition consists of a nonreactive thermoplastic polymer or copolymer dissolved or dispersed in an organic solvent. This polymeric solution is placed into the body where the polymer gels or precipitatively solidifies upon the

dissipation or diffusion of the solvent into the surrounding body tissues. Also, improved polymeric compositions that form a solid matrix in situ thereby forming an implant for sustained release of a medicament over a desired period of time are described in the patent literature.

An example of a commercially available product that utilizes this technology is the ATRIDOX™ product which is a subgingival controlled-release product composed of a two syringe mixing system. Syringe A contains 450 mg of the ATRIGEL® Delivery System, which is a bioabsorbable, flowable polymeric formulation composed of 36.7% poly(DL-lactide)(PLA) dissolved in 63.3% N-methyl-2-pyrrolidone (NMP). Syringe B contains the antibiotic doxycycline hyclate which is equivalent to 42.5 mg doxycycline.

K.P. Andriano et al., J. Biomed. Mater. Res. (Appl. Biomater.), 53: 36-43 (2000), disclose preliminary *in vivo* studies on the osteogenic potential of bone morphogenetic proteins delivered from an absorbable puttylike polymer matrix. R.L. Dunn et al., Portland Bone Symposium 1999, Oregon Health Sciences University, pages 522 to 528, studied the osteoinductivity of bone morphogenetic proteins delivered from an absorbable putty-like matrix.

The optimal control of release rate of certain bone growth promoting compounds, especially certain small molecule, is a never-ending quest for sustained release implants including but not limited to the flowable compositions. Consequently, there is the need for a flowable composition in which the rate of delivery of certain bone growth promoting compounds can be more readily controlled, especially for a compound which requires sustained release over a longer time period.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide improved polymeric compositions in which the rate of release of a bone growth promoting compound is balanced against the rate of degradation of the polymer. It is a further object of the present invention to provide improved polymeric compositions which form an implant in situ that degrades quickly enough so as to not impede bone growth at the desired site.

The present invention provides the following:

A pharmaceutical composition suitable for in situ formation of an implant in a patient comprising:

(a) a pharmaceutically acceptable, biodegradable thermoplastic polymer or copolymer that is insoluble in aqueous or body fluid;

(b) a biocompatible organic solvent which solubilizes the thermoplastic polymer, is dispersible in situ in body fluid, is highly soluble in water and is capable of dissipating from the polymer system into surrounding tissue fluid whereupon the thermoplastic polymer forms the implant; and

(c) a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof selected from the group consisting of:

(3-(((4-*tert*-butyl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenoxy)-acetic acid;

7-[(4-butyl-benzyl)-methanesulfonyl-amino]-heptanoic acid; and

7-{[2-(3,5-dichloro-phenoxy)-ethyl]-methanesulfonyl-amino}-heptanoic acid.

More particularly, the present invention provides the above composition wherein the composition forms a controlled release implant at or near the site of local administration. Also, the present invention provides the above composition wherein the composition forms a controlled release implant at or near the site of the bone fracture, bone injury or bone defect.

More particularly, the present invention provides the above composition wherein the compound is the sodium salt of (3-(((4-*tert*-butyl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenoxy)-acetic acid. Also, the present invention provides the above composition wherein the compound is the free acid of (3-(((4-*tert*-butyl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenoxy)-acetic acid.

More particularly, the present invention provides the above composition wherein the amount of the compound is between about 5 to about 50 mgA/ml of the composition. Even more particularly, the present invention provides the above composition wherein the amount of the compound is about 5, 10 or 50 mgA/ml of the composition.

More particularly, the present invention provides the above composition wherein the polymer is selected from the group consisting of polylactides, polyglycolides and copolymers thereof. More particularly, the present invention provides the above composition wherein the copolymer has an inherent viscosity of about 0.20 dl/g to about 0.40 dl/g. Even more particularly, the present invention provides the above composition wherein the copolymer has an inherent viscosity of about 0.20 dl/g.

More particularly, the present invention provides the above composition wherein the copolymer is poly-lactic-co-glycolic acid (PLGH). Even more particularly, the present invention provides the above composition wherein the ratio of lactic acid to glycolic acid is about 1 to about 1.

More particularly, the present invention provides the above composition wherein the copolymer is polyethylene glycol (PEG) end-capped poly-lactic-co-glycolic acid (PLGH). Even more particularly, the present invention provides the above composition wherein the weight % of PEG to PLGH is between about 3 to about 5%.

More particularly, the present invention provides the above composition wherein the solvent is N-methyl-2-pyrrolidone (NMP). Even more particularly, the present invention provides the above composition wherein the copolymer is poly-lactic-co-glycolic acid (PLGH) and wherein the solvent is N-methyl-2-pyrrolidone (NMP). The present invention provides such composition wherein the weight percentage of PLGH to NMP in solution is between about 30% and about 60% of PLGH to between about 70% and about 40% of NMP. Even more particularly, the present invention provides the above composition wherein the weight percentage of PLGH to NMP in solution is selected from the following: about 37% PLGH to about 63% NMP; about 45% PLGH to about 55% NMP; about 50% PLGH to about 50% NMP; and about 55% PLGH to about 45% NMP. Most particularly, the present invention provides the above composition wherein the weight percentage of PLGH to NMP in solution is about 50% PLGH to about 50% NMP.

In addition, the present invention provides a pharmaceutical kit suitable for in situ formation of a biodegradable implant in the body of a patient, which comprises:

A) a device containing a compound or a pharmaceutically acceptable salt thereof selected from the group consisting of:

(3-(((4-*tert*-butyl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenoxy)-acetic acid;

7-[(4-butyl-benzyl)-methanesulfonyl-amino]-heptanoic acid; and

7-{[2-(3,5-dichloro-phenoxy)-ethyl]-methanesulfonyl-amino}-heptanoic acid; and

B) a device containing a flowable composition of a biodegradable, biocompatible, pharmaceutically acceptable thermoplastic polymer that is insoluble in aqueous or body fluid and a pharmaceutically acceptable solvent that is dispersible in situ in body fluid and is highly water soluble, wherein the

concentrations and formulas of the polymer and the solvent in the flowable composition are effective to form an implant in situ when the flowable composition contacts body fluid;

C) wherein the devices have an outlet for the compound or the flowable composition, an ejector for expelling the compound or the flowable composition through the outlet and a hollow tube fitted to the outlet; and wherein the contents of the two devices are mixed together immediately prior to delivering the contents of the device containing the mixture into the body of the patient.

More particularly, the present invention provides the above pharmaceutical kit wherein the concentrations and formulas of the polymer and the solvent are effective to form a space filling implant in the body of the patient.

More particularly, the present invention provides the above pharmaceutical kit wherein the polymer is selected from the group consisting of polylactides and copolymers thereof with glycolide. Even more particularly, the present invention provides the above pharmaceutical kit wherein the copolymer is poly-lactic-co-glycolic acid (PLGH). Even more particularly, the present invention provides the above pharmaceutical kit wherein the ratio of lactic acid to glycolic acid is about 1 to about 1.

More particularly, the present invention provides the above pharmaceutical kit wherein the solvent is N-methyl-2-pyrrolidone (NMP). More particularly, the present invention provides the above pharmaceutical kit wherein the compound is in the lyophilized form.

Also, the present invention provides a method of forming an implant in-situ, in a living body, comprising the steps of:

(a) dissolving a non-reactive, water-insoluble biodegradable polymer in a biocompatible, highly water soluble organic solvent that is dispersible in body fluid in situ to form a flowable composition;

(b) adding an effective amount of a compound to the flowable composition to provide a pharmaceutical composition;

(c) placing the pharmaceutical composition within the body; and

(d) allowing the solvent to dissipate to produce a solid or gel implant which releases the compound by diffusion, erosion or a combination of diffusion and erosion as the implant biodegrades;

wherein the compound or a pharmaceutically acceptable salt thereof is selected from the group consisting of:

(3-(((4-*tert*-butyl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenoxy)-acetic acid;

7-[(4-butyl-benzyl)-methanesulfonyl-amino]-heptanoic acid; and

7-{[2-(3,5-dichloro-phenoxy)-ethyl]-methanesulfonyl-amino}-heptanoic acid;

wherein the polymer is selected from the group consisting of polylactides and copolymers thereof with glycolide; and

wherein the solvent is N-methyl-2-pyrrolidone (NMP).

More particularly, the present invention provides the above method wherein the copolymer is poly-lactic-co-glycolic acid (PLGH). More particularly, the present invention provides the above method which further comprises delivering said liquid in-situ through a syringe. More particularly, the present invention provides the above method wherein the implant is formed at or near a bone fracture, bone defect or bone injury in the body. Also, the present invention provides a biodegradable drug delivery implant for a body produced according to the above method.

In addition, the present invention provides a kit for achieving a therapeutic effect in a mammal which has been prescribed the joint administration of the ingredients designated as (1) and (2) below, each ingredient forming a portion of said kit, comprising in association:

(1) a therapeutically effective amount of an active ingredient, said active ingredient being (3-(((4-*tert*-butyl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenoxy)-acetic acid; 7-[(4-butyl-benzyl)-methanesulfonyl-amino]-heptanoic acid; or 7-{[2-(3,5-dichloro-phenoxy)-ethyl]-methanesulfonyl-amino}-heptanoic acid; or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent in a first unit dosage form;

(2) a flowable composition of a biodegradable, biocompatible, pharmaceutically acceptable thermoplastic polymer that is insoluble in aqueous or body fluid and a pharmaceutically acceptable, highly water soluble solvent that is dispersible in situ in body fluid, wherein the concentrations and formulas of the polymer and the solvent in the composition are effective to form an implant in situ when said composition contacts body fluid; in a second unit dosage form; and

(3) directions for the administration of the ingredients (1) and (2) in a manner to achieve the desired therapeutic effect.

More particularly, the present invention provides the above kit wherein the active ingredient is the sodium salt of (3-(((4-*tert*-butyl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenoxy)-acetic acid. More particularly, the present invention provides the above kit wherein the active ingredient is the free acid of (3-(((4-*tert*-butyl-benzyl)-(pyridine-3-sulfonyl)-amino)-methyl)-phenoxy)-acetic acid.

More particularly, the present invention provides the above kit wherein the polymer is selected from the group consisting of polylactides, polyglycolides and copolymers thereof. Even more particularly, the present invention provides the above kit wherein the polymer is selected from the group consisting of polylactides and copolymers thereof with glycolide. Even more particularly, the present invention provides the above kit wherein the copolymer is poly-lactic-co-glycolic acid (PLGH). Even more particularly, the present invention provides the above kit wherein the ratio of lactic acid to glycolic acid is about 1 to about 1.

More particularly, the present invention provides the above kit wherein the solvent is N-methyl-2-pyrrolidone (NMP). Also, the present invention provides the above kit wherein the compound is in the lyophilized form.

The present invention is directed to a polymer system for specific bone growth promoting compounds, a method for therapeutic treatment using such polymer system and a precursor of such polymer system, a flowable composition.

The present invention provides a flowable composition that provides sustained release at the local site of injection (e.g., bone fracture site, bone defect site, bone injury site) by forming a biodegradable solid or gel implant. More particularly, the present invention provides a composition and method for delivering a bone growth promoting compound in a slow-release biodegradable polymer based delivery system, which is preferably injectable.

The polymer system is a microporous, solid or gel matrix of a biocompatible, biodegradable thermoplastic polymer and a bone growth promoting compound. The system of the present invention provides for optimal control of the rate and extent of release of the bone growth promoting compound from the matrix. The flowable composition contains an organic solvent, a biocompatible, biodegradable thermoplastic polymer and a bone growth promoting compound.

The polymer system is formed by applying the flowable composition to either of two gelation media: a) body fluid that is internal to the body, and b) a water medium that is external to the body. After application, the flowable composition gels or

coagulates to form the polymer system. Administration of the flowable composition directly into the body forms in situ the polymer system. External addition of the flowable composition to a water medium forms the polymer system outside the body. The solid implantable polymer system formed outside the body can then be surgically placed into the body. In all embodiments and applications, the polymer system is substantially insoluble in water, water solutions and body fluid.

The process by which the polymer system is formed in part is responsible for development of the rate and release control. Interaction of the flowable composition with body fluid in situ in the body to coagulate or gel the composition into the polymer system at least in part causes the desired controlled release profile as a function of the variation of the below-mentioned parameters and components. Simple combination of these components without passage through the flowable composition will not develop the controlled release profile of the present invention. When the flowable composition is contacted by body fluid *in situ*, the organic solvent diffuses into the surrounding medium (body fluids) and the polymer coagulates or gels to form the solid or gel matrix (polymer system). Because the body fluid contains lipophilic components and dynamically flows around the flowable composition, the coagulation or gelling occurs when the organic solvent has a water solubility ranging from highly soluble to insoluble.

When the composition of the present invention is placed in the body, it is retained locally at the site of the fracture, defect or injury. The resulting polymer system may adopt the shape of the bone fracture, defect or injury into which the composition is placed.

Pursuant to the parameters and conditions of the present invention, the polymer system can control the sustained release of a bone growth promoting compound in vivo. In particular, the rate and extent of release of the bone growth promoting compound from the polymer system of the present invention are controlled over a narrow range of speeds and amounts. This control is accomplished by variation of: (a) the polymer type and molecular weight, (b) the concentration of the polymer, (c) the concentration of the bone growth promoting compound, and (d) the form of the bone growth promoting compound. Preferably, the rate and extent of release of the bone growth promoting compound from the polymer system according to the present invention can be controlled by varying: (1) the type and molecular weight of the polymer or polymers, and/or (2) the concentration of the polymer.

More preferably, the control is accomplished by varying the molecular weight of the polymer. In preferred embodiments, the rate of release increases as polymer molecular weight decreases.

The method of the present invention is based upon the therapeutic effect of the in situ controlled release of the bone growth promoting compound from the polymer system. The implantation of the flowable composition occurs at or near the site of the bone fracture, bone defect or bone injury in the body of a patient in need of therapeutic treatment. For example, it may be implanted in the bone fracture so that it adapts and conforms to the shape of the fracture. Preferably, it is implanted in the soft tissue, such as muscle or fat, at or near the site of the bone fracture, defect or injury. The composition can be administered to the implant site by any suitable method for applying a flowable composition, as for example, by means of a syringe, needle, cannula or catheter. The polymer system preformed as an implant can be inserted by known surgical techniques.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a polymer system for the controlled delivery of a bone growth promoting compound, a flowable composition for producing such system, and a method for use of such a system in therapeutic treatment. The polymer system of the present invention is advantageous in that it can be manipulated to control the amount of bone growth promoting compound released and the rate at which it is released in vivo.

The present invention provides an injectable, flowable composition that provides sustained release at the local site of the injection (e.g., bone fracture site, bone defect site, bone injury site) by forming a biodegradable solid or gel depot, matrix or implant.

More particularly, the present invention provides a composition and method for delivering a bone growth promoting compound in a slow-release biodegradable polymer based delivery system.

The polymer based delivery system contains a bone growth promoting compound dissolved or dispersed in biodegradable, thermoplastic polymer solution or dispersion in an organic solvent. Upon injection of the flowable composition, the organic solvent diffuses away from the injection site, causing the polymer to precipitate or gel; thereby entrapping the compound in a sustained-release depot. The compound is subsequently released by diffusion from, and erosion of, the

INTERNATIONAL SEARCH REPORT

Intern: Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 27962 A (ALZA CORP ;SHEN THEODORE T (US); BRODBECK KEVIN J (US)) 2 July 1998 (1998-07-02) page 7, line 1 -page 8, line 2 page 8, line 21 - line 29 page 15, line 4 - line 15 page 16 -page 17; examples claims	1-15
A	WO 95 28124 A (ATRIX LAB INC) 26 October 1995 (1995-10-26) page 3, line 13 - line 22 page 10, line 14 -page 11, line 14 page 22, line 19 -page 23, line 4 page 30, line 9 -page 32, line 28; examples claims page 8, line 13 -page 9, line 4	1-15
A	EP 0 950 403 A (ATRIX LAB INC) 20 October 1999 (1999-10-20) page 1, paragraph 5 - paragraph 8 page 5, paragraph 31 page 6, line 53 - line 54 page 7, paragraph 48 - paragraph 49 page 8 -page 10; examples claims	1-15
Y	WO 99 19300 A (ROSATI ROBERT LOUIS ;PFIZER (US); CAMERON KIMBERLY O KEEFE (US); L) 22 April 1999 (1999-04-22) cited in the application page 1, line 1 - line 7 page 18, line 18 - line 21 page 92, line 20 - line 29 page 98, line 15 -page 99, line 2 page 102, line 21 - line 28 page 105 -page 107 page 116; example 1AA	1-15
Y	WO 98 28264 A (ROSATI ROBERT LOUIS ;KE HUA ZHU (US); PFIZER (US); CAMERON KIMBERL) 2 July 1998 (1998-07-02) cited in the application page 1, line 1 - line 7 page 12, line 18 page 18, line 20 - line 21 page 97, line 15 - line 29 page 102, line 14 -page 104, line 32 page 114, line 10 -page 115, line 17 page 121, line 1-11 page 121, line 21 - line 25	1-15